

propagation initiates self-sustaining periodic behavior at the leading edge. The model and experiment are in quantitative agreement.

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Force Transmission in Migrating Cells: Gripping at the Front, Slipping at the Back

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During cell migration, forces generated by actin cytoskeleton are transmitted through adhesion complexes to the substrate. To investigate the mechanism of force generation and transmission, we analyzed the relationship between the velocity of actin network movement and the stress applied to the substrate over the entire cell using a simple model of persistently migrating fish epidermal keratocytes. Lateral stresses at the cell sides and forward stress at the back of the cell were largely proportional to actin velocity, with higher coefficient of proportionality for lateral stresses than for the forward stress. In contrast, backward propulsive stress at the cell front exhibited significant velocity independent component. These results suggested that the mechanism of conversion of actin dynamics into the substrate stress depended on the region of the cell and on the direction of the stress: frictional slippage was characteristic of the back and sides of the cell, and elastic gripping, of the front. Analysis of substrate stress and cell motion in the presence of inhibitors of actin/myosin system cytochalasin D and blebbistatin indicated that cell translocation could be driven by two different processes: actomyosin contraction, and actin assembly, the former associated with significantly larger substrate forces than the latter.

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Continuum Elastic Model of Epithelial Sheet Migration

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A key component of a wound healing process is rapid migration of epithelial cells that covers the wound area and helps to protect the underlying tissue. In our recent paper* we have developed a one-dimensional continuum mechanical model of intestinal epithelial cell layer, that incorporates lamellipod forces at both the wound edge and in the interior of the layer, adhesion forces between the cell layer and the substrate, and elastic stress within the cell layer. Here, the model is extended to two-dimensions and solved numerically using a level set method, which tracks the moving wound edge on a fixed grid. The model is calibrated by comparing the position of wound edge with experimentally observed positions in scratch-wound assay experiments. These comparisons show good qualitative agreement between model results and experimental observations. The models supports experimental observations that the time to wound closure varies with initial wound shape and area, and that the closure is possible, albeit slower, if boundary lamellipod formation is inhibited.

* Qi. et al., One-dimensional elastic continuum model of enterocyte layer migration, *Biohys. J.*, **93**, 3745-3752 (2007).

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Biophysical Regulation of Astrocytoma Cell Physiology in 2D and 3D Culture

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The rapid progression of high-grade brain tumors is related to diffuse infiltration of single tumor cells into the surrounding brain parenchyma, a process that involves aberrant interactions between tumor cells and the extracellular matrix (ECM). Here, we show that biophysical cues from the ECM regulate key tumor cell properties relevant to invasion in both two-dimensional (2D) and three-dimensional (3D) culture models. We first investigated the role of ECM rigidity in regulating the structure, migration, and proliferation of a panel of astrocytoma cell lines on 2D fibronectin-coated polymeric ECM substrates of defined mechanical rigidity. On highly compliant ECMs, tumor cells appear rounded and fail to productively migrate. As ECM rigidity is increased, tumor cells spread extensively, form prominent stress fibers and mature focal adhesions, and migrate rapidly. Remarkably, cell proliferation is greatly enhanced

on rigid versus compliant ECMs. Pharmacological inhibition of nonmuscle myosin II-based contractility blunts this rigidity-sensitivity and rescues motility on highly compliant substrates. We next explore astrocytoma mechanosensitivity in 3D by introducing a novel biomaterial platform in which we progressively modulate the biophysical properties of collagen I matrices by adding agarose. We find that agarose increases the bulk elasticity of 3D collagen ECMs over two orders of magnitude by forming a dense meshwork that intercalates between the entangled collagen fibers. Embedded glioma cells exhibit a pronounced transition to amoeboid motility accompanied by severe limitation of cellular invasion from multicellular spheroids as the agarose content of the hydrogels increases from 0-1% w/v. Our results are consistent with a model in which agarose structurally couples and reinforces individual collagen fibers, simultaneously introducing steric barriers to cell motility while shifting ECM dissipation of cell-induced stresses from the non-affine deformation of individual collagen fibers to the bulk-affine deformation of a continuum network.

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Numerical Simulation of Myosin-Triggered Switch in Motile Cells

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Force generation and movement in motile cells are a result of coordinated spatial-temporal organization and segregation of some essential proteins including myosins and integrins. Biochemical signaling coupled with transport underlines the self-organizations of such proteins. It is also expected that the mechanical deformation and restructuring of cell cytoskeleton plays an important role. This is particularly true with proteins that bind and interact directly with cytoskeleton such as myosins and integrins. To see how myosin and adhesion organization is influenced by cytoskeletal dynamics, we use computational modeling to examine simple continuum models of f-actin network mechanics interacting with myosin. We restrict our study to fish keratocyte since it has a highly symmetric and stable shape as it moves. We find that (i) the distribution of myosin is characterized by the left-right symmetry and is biased to the rear; (ii) the f-actin flow induced by myosin contraction is graded (highest at the rear and minimal at the front), (iii) adhesion density is biased to the cell rear and is in antagonistic relation with f-actin. Moreover, there is an effective dynamic switch in cell motile behavior triggered by the overall adhesion/myosin strength. The modeling results are consistent with experimental findings (data courtesy of Julie Theriot group).

Microtubule Motors-Kinesin-related Proteins

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Spindle and Pole Mechanisms in Bipolarity and Prophase Control of Spindle Elongation

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Genomic stability through cell division in eukaryotes is enhanced by formation of a conserved mitotic spindle apparatus regulated by multiple Kinesin-like motor protein (Klp) families. While Kinesin-5 and Kinesin-14 opposing forces provide a ubiquitous balance to spindle assembly and stability, Kinesin-6 Klp also contribute. When domain specialization in Kinesin-14 members favors pole localization and mechanisms, Kinesin-6 Klp can provide critical regulation of prophase microtubule cross-linking and spindle elongation. By genetic, cell biological and biochemical approaches including cross-species analysis with human HSET, *Drosophila* Ncd and *Schizosaccharomyces pombe* Pkl1 we are characterizing Klp structure and function in balancing bipolar spindle assembly with regulation of spindle elongation in prophase. HsHSET functionally replaces SpPkl1 in fission yeast, displays similar localization to poles in prophase, and is unable to oppose bipolarity in the presence of a γ -tubulin mutation in a defined Kinesin-14 binding site. DmNcd does not replace SpPkl1 and localizes preferentially to bundled interpolar spindle microtubules, unlike the more uniform spindle and prominent pole localization of HsHSET and SpPkl1. By in vivo analysis of thirty Kinesin-14 derivatives, including Tail, Stalk or Neck-Motor chimeras, for spindle assembly, spindle localization and mitotic progression we defined critical Tail domain regions in SpPkl1 for establishing bipolarity. In fission yeast, Kinesin-6 and Kinesin-14 Pkl1 oppose each other both in regulating bipolarity and in control of prophase spindle length. Flexibility in the design plan of Kinesin-14s, in part through varying Tail elements, broadens their mechanistic possibilities in eukaryotes that include distinct roles in spindle assembly and maintenance. Additional mitotic Klp families, like Kinesin-6, can contribute to critical mechanisms in prophase for spindle assembly and regulation of spindle length to provide the appropriate temporal balance of forces.